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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,103	08/18/2003	Klaus Gregorius Nielsen	674542-2015	3313

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,103	NIELSEN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/06/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group II (claims 23-32) in the Reply filed 24 April 2006 is acknowledged. The traversal is on the grounds that searches of Groups I and II would be co-extensive and thus do not represent a search burden.

Applicants' argument has been fully considered and is not found to be persuasive. Applicants' attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation of one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search."

As set forth in the Restriction requirement of 22 March 2006, Group I is classified in class 424, subclass 184.1 and Group II is classified in class 424, subclass 130.1. The separate classification established for each Group demonstrates that each distinct Group has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Thus, the Restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-22 are hereby withdrawn from consideration as being drawn to a non-elected invention. Currently, claims 23-32 are under consideration.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed 06 December 2005 is enclosed in this action.

Specification

The disclosure is objected to because of the following informalities: P.1, line 8 contains the typo "Augusts".

Appropriate correction is required.

The use of trademarks has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objections

Claims 23-32 are objected to because of the following informalities: The claims depend from non-elected claims.

Claim 23 contains the typo "with a pharmacologically an immunologically acceptable carrier."

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-32 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are directed to a method for immunizing an animal against an antigen of choice, comprising administering an effective amount of the immunogen which comprises at least one antigenic determinant constituted by an amino acid sequence that includes at least one B-cell epitope and/or at least one CTL epitope, and at least one second antigenic determinant constituted by an amino acid sequence that includes a T helper cell epitope (T_H epitope), or administering an effective amount of an immunogenic composition for raising an immune response.

These are genus claims because they are directed to a plurality of undisclosed amino acid molecules. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual

reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural features of the genus of amino acid sequences such that they would be functional in the claimed methods. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the amino class are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, any amino acid sequence comprising B-cell and/or CTL epitopes and any amino acid comprising TH epitopes is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants are not in possession of the claimed genus.

Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering an immunogen comprising either Aβ-42 or the *Borrelia burgdorferi* protein OspC as peptide A and a diphtheria toxoid epitope (P2 or P30) as peptide B, does not reasonably provide enablement for methods of immunizing an animal with immunogens comprising any amino acid sequence that includes a B cell and/or CTL epitope and any amino acid sequence that includes a T_H epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are directed to a method for immunizing an animal against an antigen of choice, comprising administering an effective amount of the immunogen which comprises at least one antigenic determinant constituted by an amino acid sequence that includes at least one B-cell epitope and/or at least one CTL epitope, and at least one second antigenic determinant constituted by an amino acid sequence that includes a T helper cell epitope (T_H epitope), or administering an effective amount of an immunogenic composition for raising an immune response.

The potential amino acid sequences encompassed by the claims have particular structures and functions, the predictability of which is complex and outside the realm of routine experimentation. Since detailed information regarding the structural requirements of the multitude of potential amino acid sequences encompassed by the claims are lacking and given the lack of working examples reciting any and all of said sequences, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicants are required to enable one of skill in the art to practice the claimed invention; while the claims encompass methods of immunizing an animal with an immunogen that comprises a plurality of undisclosed amino acid sequences, the specification only teaches one skilled in the art to make and use immunogens with either Aβ-42 or the *Borrelia burgdorferi* protein OspC as peptide A and a diphtheria toxoid epitope (P2 or P30) as peptide B. Thus, the skilled artisan would not be assured that any or all of the potential amino acid sequences encompassed by the claims would function like the peptides disclosed at pp.39-41 of the specification.

Accordingly, it is well known in the art that even two polypeptides differing in structure by only one amino acid residue can have completely different functions. For example, Mickle et al. (Med Clin North Am. 2000 May; 84(3): 597-607) teaches that cystic fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CTFR) (p.597). In this polypeptide channel, a mutation of a single glycine to aspartic acid at position 551, gives rise to the CF phenotype. Also, a single phenylalanine deletion at position 508 gives rise to the CF phenotype, thus showing that

even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein.

Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and thus the architecture of an entire cell. For example, Voet et al. (Biochemistry. 1990. John Wiley & Sons, Inc. 126-129 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pp.126-128, section 6-3A and page 230, column 2, first paragraph). Also, Yan et al. (Science 290: 523-527, 2000) teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another. Thus, as outlined *supra*, the predictability of amino acid sequences that would function as claimed is complex and outside the realm of routine experimentation.

Furthermore, relevant art regarding vaccine development teaches that the process is complex and also requires extensive experimentation. De Groot (Drug Discov Today. 2006 Mar; 11(5-6): 203-9) teaches that immunomics involves searching for the antigens and mapping the epitopes that stimulate an immune response. This is accomplished by isolating proteins from whole cells and then digesting them to find epitopes that stimulate a B-cell or T-cell response or by immunomics tools such as T-

cell and B-cell-epitope mapping algorithms. The latter method involves mathematical analyses of the patterns of amino acids that occur in peptides bound to human leukocyte antigen (HLA) by antigen-presenting cells. De Groot cautions that not all epitope-mapping tools are equivalent and teaches that few B-cell-epitope mapping algorithms are in current use and that only a handful of these tools have been validated *in vitro* or *in vivo* (p.203). De Groot also outlines the substantial experimentation necessary in order to identify potential epitope sequences that even still need to be evaluated *in vitro* or *in vivo* before a potential vaccine can be developed (e.g., Figure 1). In addition, Purcell et al. (J Pept Sci. 2003 May; 9(5): 255-81) teach "the identification of the vast majority of physiologically relevant epitopes derived from pathogens, tumours and tissues targeted by aberrant autoimmune responses, however, remain undefined. Coupled with the extensive polymorphism exhibited by HLA molecules this creates a challenge for the incorporation of minimal peptide epitopes into immunotherapeutics and diagnostics. Thus, a combination of bioinformatics, analytical biochemistry and peptide based validation studies needs to be applied to identify useful lead compounds by subsequent exploitation by peptide chemistry."

Also, even when vaccines show potential through induction of a substantial immune response as defined by the antigen antibody titer, they can lack effectiveness in the clinical setting (see Hanke, Eur J Immunol. 2006 Apr; 36(4): 806-9). In one example regarding a hepatitis B vaccine, "various multivalent combinations of vaccines with drugs and cytokines are being explored to overcome the non-responsiveness to the prophylactic vaccine and to boost and broaden weak HBV-specific T-cell responses in

patients with chronic hepatitis B." Accordingly, although some of these techniques are thought to be promising, the results in early clinical trials have been unimpressive (p.807), thus further supporting the unpredictability of the claimed methods.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to establish a nexus between methods of immunizing an animal and immunogens comprising the plurality of amino acid sequences encompassed by the claims, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass variant proteins, undue experimentation would be required of the skilled artisan to make and use the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-27 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,656,451 to Flavell et al.

The claims are directed to a method for immunizing an animal against an antigen of choice, comprising administering an effective amount of the immunogen which comprises at least one antigenic determinant constituted by an amino acid sequence that includes at least one B-cell epitope and/or at least one CTL epitope, and at least

one second antigenic determinant constituted by an amino acid sequence that includes a T helper cell epitope (T_H epitope), or administering an effective amount of an immunogenic composition for raising an immune response.

The '541 patent discloses methods of immunizing an animal, including a human, against *Borrelia burgdorferi* infection with therapeutically effective amounts of vaccines to one or more *Borrelia burgdorferi* polypeptides (including OspC), which comprise T helper cell and/or B-cell epitopes (col.6, lines 50-60; col.9, lines 20-50; col.12, line 26 – col.14, line 20) and discloses immunogenic compositions comprising the immunogen and pharmaceutically acceptable carriers, excipients, diluents and adjuvants (col.19, line 22 – col.20, line 36). The '541 patent also discloses immunogenic peptides linked to carriers at the amino terminus or carboxyl terminus (col. 10, line 67; col. 17, lines 40-42) and discloses peptidases (col.24, line 35) and polyhydroxyl polymers such as dextran, agarose, polyacrylamide, and polyethylene glycol (col.19, line 49; col.21, lines 29-31). Thus, as outlined *supra*, the limitations of claim 23 have been taught by the '541 patent.

The '541 patent also discloses that the administration of the immunogen/compositions may be parenteral, topical, intracutaneous, subcutaneous, oral, intramuscular (which encompasses buccal), intrathecal (which encompasses epidural and spinal) and through suppositories (which encompasses anal; col.19, line 32 – col.20, line 11), thus meeting the limitations of claim 24. Further, the administration may be in the range of 10µg -100 mg, preferably 100-1000 µg, per patient (col.20, lines 25-28) and at least two times a year (col.19, lines 18-21), thus

meeting the limitations of claims 25-27. Since the patent discloses all the elements of the claims, claims 23-27 are anticipated by U.S. Patent No. 5,656,451 to Flavell et al.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-32 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,787,637 to Schenk (cited in Applicants' IDS from 06 December 2005).

The claims are directed to a method for immunizing an animal against an antigen of choice, comprising administering an effective amount of the immunogen which comprises at least one antigenic determinant constituted by an amino acid sequence that includes at least one B-cell epitope and/or at least one CTL epitope, and at least one second antigenic determinant constituted by an amino acid sequence that includes a T helper cell epitope (T_H epitope), or administering an effective amount of an immunogenic composition for raising an immune response.

The '637 patent discloses methods of treating and preventing (immunizing against; col.25, lines 38-45) a disease associated with amyloid deposits of Aβ in the brain of a human and non-human patient (col.26, lines 42-44) including but not limited to Alzheimer's disease and/or Down's syndrome, comprising administering an effective amount (col. 26, lines 32&33) of an immunogenic Aβ fragment (including Aβ-42) conjugated to a T helper cell and/or B-cell epitope (col. 3, lines 15-65; col.11, lines 1-65). The patent also discloses immunogenic compositions comprising the immunogen

and pharmaceutically acceptable carriers, excipients, diluents and adjuvants (col.29, lines 24-51). Immunogenic peptides linked to carriers at the amino terminus, carboxyl terminus, or both (col. 21, lines 13-16) are disclosed, as are pharmaceutically acceptable polyhydroxyl polymers such as agarose, cellulose and polymeric amino acids (col.29, lines 42-51). It is noted that the limitation of "via a bond that is cleavable by a peptidase" is not given patentable weight, since polypeptides (which consist of many peptide bonds) are cleavable by peptidases along the length of the molecules. Therefore, the '637 patent inherently meets this limitation. Thus, as outlined *supra*, the limitations of claim 23 have been taught by the '637 patent.

The '637 patent also discloses that the administration of the immunogen/compositions may be parenteral, topical, peritoneal, oral, intracranial, intramuscular (which encompasses buccal), suppositories (which encompasses anal) or by means of a sustained release device (which encompasses a VLN; col.27, lines 40-57; col.30, line 20), thus meeting the limitations of claims 24 and 32. Further, the administration may be once a year, 4 times a year, to once a day in the range of 1-500 μg per patient (col. 26, lines 36-65), thus meeting the limitations of claims 25-31. Since the patent discloses all the elements of the claims, claims 23-32 are anticipated by U.S. Patent No. 6,787,637 to Schenk.

Conclusion

No claims are allowed.

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 9AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph. D.
Patent Examiner
Art Unit 1649
24 May 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER